CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

PICARIDIN

Chemical Code # 5908, **Tolerance #** 52978
SB 950 # NA

April 4, 2005

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, possible adverse effect indicated
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	No data gap, no adverse effect

Toxicology one-liners are attached.

All record numbers through 217394 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T050404
Revised by T. Moore, 4/4/05

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

** 0011, 0030; 212268, 217393; "Technical Grade KBR 3023: A Combined Chronic Toxicity/Oncogenicity Testing Study in the Rat"; (B.S. Wahle, W.R. Christenson; Bayer Corporation, Agriculture Division, Toxicology, Stilwell, KS; Report No. 107432; 12/17/96); The skin of 50 Sprague-Dawley rats/sex/group was treated with 0, 50, 100 or 200 mg/kg/day of KBR 3023 Technical (batch no. 030693; purity: 98.2 (6/93), 98.5 (12/93), 98.1 (6/94), 97.7 (2/95), 97.4 (8/95), 96.7% (3/96)) 5 days per week for 2 years (the two year cohort). Additionally, 20 animals/sex/group were treated with 0 or 200 mg/kg/kg and 10 animals/sex/group were treated with 50 or 100 mg/kg/day of the test material. These animals received the treatment for one year (one year cohort). There was no apparent effect of an increased mortality due to the treatment. There was no treatment-related effect upon mean body weight, food consumption, clinical signs, ophthalmology, hematology, clinical chemistry, urinalysis, absolute or relative organ weights, or histopathology. **No adverse effect indicated. Chronic Dermal Toxicity NOEL:** (M/F) 200 mg/kg/day (based upon the lack of a treatment-related effect at the highest dose tested); **Oncogenicity not evident**. Study previously unacceptable, not upgradeable because the reviewer did not consider that the dosing regimen had adequately evaluated the oncogenic potential. In document no. 52978-0030, rec. no. 217393, the registrant provided their rationale as to why a higher dose level could not be achieved. (Moore, 10/12/04, upgraded, Moore, 3/22/05))

CHRONIC TOXICITY, RAT

See Combined Rat, above.

CHRONIC TOXICITY, DOG

** 0010; 212265; "Technical Grade KBR 3023: A Chronic Percutaneous Toxicity Study in the Beagle Dog"; (R. D. Jones, T.F. Hastings; Bayer Corporation, Agriculture Division, Toxicology, Stilwell, KS; Report No. 107155; 12/1/95); The skin of 4 beagle dogs/sex/group was treated with 0, 50, 100 or 200 mg/kg of Technical Grade KBR 3023 (batch no. PT030693, purity: 98.2% (6/93), 98.5% (12/93), 98.1% (6/94)) 5 days/week for 12 months. The test material was placed on the back of each animal in a depilated area not available to grooming. There was no treatment-related effect evident in the mean body weight or food consumption data. No treatment-related clinical signs were apparent. No treatment-related effects were evident in the hematology, clinical chemistry, the liver enzyme assays, and the urinalysis. In the necropsy and micropathology examinations, no treatment-related effect was noted for the mean absolute or relative organ weights and no treatment-related lesions were evident. **No adverse effect evident. Chronic Dermal Toxicity NOEL:** (M/F) 200 mg/kg/day (based upon the lack of a treatment-related effect at the highest dose tested); **Study acceptable.** (Moore, 10/7/04)

ONCOGENICITY, RAT

See Combined Rat, above

ONCOGENICITY, MOUSE

** 0012, 0030; 212269, 217393; "Technical Grade KBR 3023: An Oncogenicity Dermal Toxicity Study in the Mouse"; (B.S. Wahle, W.R. Christenson; Bayer Corporation, Agriculture Division, Toxicology, Stilwell, KS; Report No. 107433; 12/18/96); The skin of fifty CD-1 mice/sex/group was treated with 0, 50, 100 or 200 mg/kg/day of KBR 3023 Technical (batch no. 030693; purity: 98.5 (12/93), 98.1 (6/94), 97.7 (2/95), 97.4 (8/95)) 5 days per week for 18 months. There was no apparent effect of an increased mortality due to the treatment. There was no treatment-related effect upon mean body weight, food consumption, clinical signs, hematology (including differential white blood cell count and cell morphology), and absolute or relative organ weights. In the histopathology examination, there was an increased incidence of amyloid deposits for the treated skin of the females in the 100 and 200 mg/kg groups ($p<0.05$). **No adverse effect indicated. Chronic Dermal Toxicity NOEL:** (M/F) 200 mg/kg/day (based upon the lack of a systemic treatment-related effect at the highest dose tested); **Oncogenicity not evident**. Previously, the study was deemed to be unacceptable, not upgradeable because a maximum tolerated dose was not achieved; In document no. 52978-0030, rec. no. 217393, the registrant provided their rationale as to why a higher dose level could not be achieved. **Study acceptable.** (Moore, 10/13/04, upgraded, Moore, 3/22/05)

REPRODUCTION, RAT

** 0018; 212277; "A Two Generation Reproductive Toxicity Study with KBR 3023 Technical in the Sprague-Dawley Rat"; (A. B. Astroff; Bayer Corporation, Agriculture Division, Toxicology, Stilwell, KS; Report No. 107489; 12/18/96); The skin of 30 Sprague Dawley rats/sex/group was treated with 0, 50, 100, or 200 mg/kg/day of KBR 3023 Technical (batch no. 030693; purity: 97.7% (2/95), 97.4% (8/95), 96.7% (3/96)), 5 days/week for two generations. The treatment periods included 10 weeks prior to mating, mating, 3 weeks gestation and 3 weeks of lactation. At that time, 30 F1 animals/sex/group were selected as parents and treated for an additional 10 weeks, followed by mating and 3 weeks each for gestation and lactation of the F2 generation. There were no apparent treatment-related clinical signs related to systemic toxicity or effects upon the mean body weights and food consumption of the parental animals in either generation. At the application site, hyperkeratosis and acanthosis, apparent for even some of the control animals, increased in severity in a dose-related manner. There was no effect upon the reproductive parameters or development of the offspring in either generation. **No adverse effects indicated. Parental NOEL:** 200 mg/kg/day (based upon the lack of systemic treatment-related effects in the 200 mg/kg group); **Reproductive NOEL:** 200 mg/kg/day (based upon the lack of treatment-related effects on reproductive parameter for the animals in the 200 mg/kg group); **Developmental NOEL:** 200 mg/kg/day (based upon the lack of treatment-related effects upon the development of the offspring). **Study acceptable.** (Moore, 11/3/04)

TERATOLOGY, RAT

** 0016; 212275; "A Developmental Toxicity Study with KBR 3023 Technical in the Sprague-Dawley Rat"; (A.B. Astroff; Bayer Corporation, Agriculture Division, Toxicology, Stilwell, KS; Study No. 95-622-DI; 9/11/96); The skin of thirty mated female Sprague-Dawley rats/group was exposed to 0, 50, 200 or 400 mg/kg/day of KBR 3023 Technical (batch no. 030693, purity: 97.7% (2/95), 97.4% (8/95)) from day 0 through day 20 of gestation. The exposure was for 24 hours with additional test material added at that time. Each animal wore an Elizabethan collar throughout the study except at the time of weighing. There were no treatment-related effects upon the mean body weight gain or food consumption. The mean absolute and relative liver weights of the 400 mg/kg dams were greater than those of the control ($p<0.01$ and $p<0.05$, respectively). There was a dose related-effect on the site of application for the test material with scaling and sloughing of the skin evident at the lowest treatment level from day 6 of gestation. There were no apparent treatment-related effect upon the fetal development. **No adverse effect indicated. Maternal NOEL:** 200 mg/kg/day (based upon increased absolute and relative liver weights for the dams in the 400 mg/kg group); **Developmental NOEL:** 400 mg/kg/day (based upon no apparent treatment-related effects for the fetuses in the 400 mg/kg group); **Study acceptable.** (Moore, 10/18/04)

<u>Range-finding Teratology Studies</u>

0015; 212272; "KBR 3023: Range-Finding Study for Embryotoxic Effects on Rats after Oral Administration"; (B. Holzum; Bayer AG, Fachbereich Toxikologie, D-5600 Wuppertal 1, Germany; Study No. T5033216; 10/29/90); 25 mated female Wistar rats/group were dosed orally by gavage with 0 or 500 mg/kg/day of KBR 3023 Technical (batch no. 19009/89, purity: 99.1%) from day 6 through day 15 of gestation. No dams died as a result of the treatment. Mean body weight gain and food consumption values for the treated animals were lower than those of the control ($p<0.05$ and $p<0.01$, respectively). There were no treatment-related effects upon fetal development. **No adverse effect indicated. Study supplemental.** (Moore, 10/18/04)

0017; 122276; "A Pilot Reproductive Toxicity Study with KBR 3023 Technical in the Sprague-Dawley Rat"; (A.B. Astroff; Bayer Corporation, Agriculture Division, Toxicology, Stilwell, KS; Study No. 94-972-DA; 9/8/95); The skin of 10 Sprague-Dawley rats/sex/group was treated with either 0 or 200 mg/kg of KBR 3023 Technical (batch no. 030693, purity: 98.1% (6/94), 97.7% (2/1/95)) 5 day/week for 2 weeks during the premating period and continuing through the mating, gestation, and lactation phases. The skin of one pup/sex/litter was treated for a number of weeks after weaning. There were no treatment-related effects upon parental mean body weights or food consumption. No treatment-related effects were noted for the litter parameters or reproductive indices. No treatment-related lesions were evident in the necropsy examinations of either the parents or the pups. **No adverse effect indicated. Study supplemental** (non-guideline, dose range-finding study). (Moore, 11/1/04)

TERATOLOGY, RABBIT

** 0014; 212271; "KBR 3023: Developmental Toxicity Study in Rabbits after Dermal Application"; (B. Holzum; Bayer AG, Institute of Toxicology, D-42096 Wuppertal, Germany; Study No. T0059079. 3/22/96); The skin of 24 mated female Himalayan rabbits/group was treated with 0, 50, 100 or 200 mg/kg/day of KBR 3023 (batch no. 030693, purity: 97.8% (1/8/95), 97.8% (4/1/96)) from day 0 through day 28 of gestation. Exposure was for 24 hours with any treatment residue removed prior to the application of the next dose. Each animal wore a collar for the duration of the treatment in order to minimize any ingestion of the test material. No treatment-related deaths occurred during the study. Two females in the control group and one female in the 200 mg/kg group aborted on days 22, 29 and 26, respectively. Dermal irritation was noted at the site of application in a dose-related manner with the erythema ranging from very slight to moderate. Edema was only evident for the 200 mg/kg group and ranged from very slight to slight. Cracked skin was noted for some animals in all of the treatment groups (0: 0 vs. 50: 2 animals, 100: 4 animals, 200: 18 animals). There was a significant increase in the incidence of soft stools for the 200 mg/kg does during the study (no. of incidences/no. of animals affected) (0: 9/3 vs. 200: 91/18). There was no treatment-related effect upon fetal development. **No adverse effect indicated. Maternal NOEL:** 100 mg/kg/day (based upon the increased incidence of soft stools noted for the 200 mg/kg group); **Developmental NOEL:** 200 mg/kg/day (based upon the lack of a treatment-related effect at the highest dose tested); **Study acceptable.** (Moore, 10/15/04)

<u>Range-finding Teratology Studies</u>

0013; 212270; "KBR 3023: Range Finding Developmental Toxicity Study in Rabbits after Dermal Application"; (B. Holzum; KBR 3023: Range Finding Developmental Toxicity Study in Rabbits after Dermal Application; Study No. T6059075; 9/20/95); The skin of three mated Himalayan female rabbits/group was exposed to 0, 50, 200, 400, 700 or 1000 mg/kg/day of technical grade KBR 3023 (batch no. 030693; purity: 97.70%) from day 0 through day 28 of gestation. The animals wore collars for the duration of the treatment as a means to minimize ingestion of the test material. The test material remained on the skin for 24 hours until the next application at which time the remainder of the material was removed with a paper towel. The test material was found to spread beyond the application site, increasing the total exposure area up to 40% for the three higher treatment levels. Two of the animals in the 1000 mg/kg group demonstrated severe weight loss and were euthanized for humane reasons on days 9 and 14 of gestation, respectively. One animal in the 700 mg/kg suffered a sizable hematoma on one of its legs and was euthanized on day 22 of gestation. Erythema, very slight to slight, was evident for the animals in the 50 to 700 mg/kg groups. The surviving female in the 1000 mg/kg group exhibited moderate skin redness. Cracked skin was noted for two animals in the 400 and all of the animals in the 700 and 1000 mg/kg groups. All of the surviving animals had live fetuses. There was no apparent treatment-related effect on post-implantation loss, mean fetal weight or external fetal malformations. **Supplemental study**. (Moore, 10/13/04)

GENE MUTATION

** 0019; 212278; "Salmonella/Microsome Test"; (B.A. Herbold; Bayer AG, Fachbereich Toxicology, D-5600 Wuppertal 1, Federal Republic of Germany; Study No. T 5033207; 3/16/90); KBR 3023 technical (batch no. 19009/89, purity: 99.1%) was directly incorporated into 4 replicate cultures/treatment level of *S. typhimurium* TA98, TA100, TA1535 and TA1537 strains at levels ranging from 8 to 5000 μg/plate (both trials) under conditions of (-/+) activation and incubated for 48 hours at 37^o C. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no apparent treatment-related increase in the incidence of reverse mutation.

The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 11/4/04)

** 0019; 212280; "Mutagenicity Study for the Detection of Induced Forward Mutations in the CHO-HGPRT Assay *in Vitro*"; (S. Brendler; Bayer AG, Fachbereich Toxicology, D-5600 Wuppertal 1, Federal Republic of Germany; Study No. T 7035540; 11/13/91); Chinese hamster ovary cells were treated with KBR 3023 Technical (batch no. 190012/89, purity: 99.6%) at concentrations ranging from 125 to 1500 μg/ml for 5 hours at 37° C without activation and from 250 to 1500 ug/ml with activation. Two trials were performed with duplicate cultures for each treatment level. Following a 6 day expression period, each culture was plated into 8 100 mm dishes for resistance to 6-thioguanine. An Aroclor 1254-induced rat liver S9 fraction was used to activate the test material. There was no apparent treatment-related increase in the incidence of forward mutation. The positive control was functional. **No adverse effect indicated. Study acceptable.** (Moore, 11/5/04)

** 0019; 212284; "V79/HPRT-Test *in Vitro* for the Detection of Induced Forward Mutations"; (B. Herbold; Bayer AG, PH-PD Toxicology, Carcinogeneity and Genotoxicity, D-42096 Wuppertal, Germany; Study No. T 8068419; 10/19/99); Chinese hamster V79 cells were exposed to KBR 3023 Technical (batch no. 898711001; purity: 98.7%) at concentrations ranging from 400 to 1600 μg/ml for 5 hours at 37° C with and w/o activation. Two trials were performed with duplicate cultures for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the mutation frequency in either of the trials. **No adverse effect indicated.** The positive controls were functional. **Study acceptable.** (Moore, 11/15/04)

CHROMOSOME EFFECTS

**** 0019; 212281**; "Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells"; (R. Gudi, E. H. Schadly; Microbiological Associates, Inc., Rockville, MD; Report No. 107777; 8/4/97); Chinese Hamster Ovary cells (CHO-K_1) (CCL 61) were incubated with KBR 3023 technical (batch no. 030693; purity: 97.1%) at concentrations ranging from 63 to 4000 ug/ml under conditions of non-activation and activation at 37° C. The nonactivated samples received 20 hours of treatment. The activated samples received 4 hours of treatment followed by 8 hours of additional incubation. In both assays, the cells were incubated the last 2 hours with Colcemid prior to fixation. All of the incubations were performed with duplicate cultures. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. In a preliminary assessment, under conditions of both non-activation and activation in which the cells were treated with concentrations up to 1500 ug/ml, 90% of the cells or greater were in the M2 stage after 24 hours of incubation. In the main assay, there was an increased incidence in the percentage of cells with chromosomal aberrations under conditions of non-activation. This increased incidence was noted in conjunction with greater cell growth inhibition. The positive controls were functional. **Possible adverse effect indicated. Study acceptable.** (Moore, 11/8/04)

**** 0019; 212282**; "*In Vitro* Mammalian Chromosome Aberration Test with Chinese Hamster Ovary (CHO) Cells"; (R. Gahlmann; Bayer AG, Fachbereich Toxicology, D-5600 Wuppertal 1, Federal Republic of Germany; Study No. T 6034405; 4/30/96); Chinese hamster ovary cells were exposed to KBR 3023 technical (batch no. 190012/89; purity: 99.5%) in two trials. The cells were exposed to concentrations ranging from 4 to 100 μg/ml (non-activation) for 7, 18 or 27 hours of treatment and from 100 to 1400 μg/ml (activation). for 2 hours of treatment and an additional 5, 16 or 25 hours of incubation. In the 2nd trial, for the non-activated cultures, the cells were exposed to 400, 800 or 1200 ug/ml of the test material for 2 hours and incubated for an additional 16 hours or to 1200 ug/ml for 2 hours and incubated for an additional 25 hours. For the activated cultures, the cells were exposed to 800, 1200 or 1600 ug/ml of the test material for 2 hours and incubated for an additional 16 hours or to 1600 ug/ml for 2 hours and incubated for an additional 25 hours. Duplicate cultures were incubated for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used for metabolism of the test material. There was a treatment-related increase in the incidence of cells with chromatid or chromosomal aberrations. The positive controls were functional. **Possible adverse effect indicated**. **Study acceptable**. (Moore, 11/8/04)

DNA DAMAGE

** 0019; 212279; "Mutagenicity Test on Unscheduled DNA Synthesis in Rat Liver Primary Cell Cultures *in Vitro*"; (S. Brendler; Bayer AG, Fachbereich Toxicology, D-5600 Wuppertal 1, Federal Republic of Germany; Study No. T 3037076; 4/29/92); Primary rat hepatocyte cultures were exposed to KBR 3023 technical (batch no. 190012/89, purity: 99.6%) at concentrations ranging from 50 to 600 μg/ml in the 1st assay and from 10 to 250 ug/ml in the 2nd assay. The cells were treated for 18 to 24 hours at 37° C. Vehicle control (ethanol, 1%) and positive control (2-acetyl-aminofluorene, 0.5 μg/ml) cultures were included in the assay. There were 3 cultures per treatment level. There was no treatment-related increase in unscheduled DNA synthesis as ascertained by autoradiography. The positive control was functional. **No adverse effect indicated. Study acceptable.** (Moore, 11/4/04)

** 0019; 212283; "Micronucleus Test on the Mouse"; (B. Herbold; Bayer AG, Fachbereich Toxicology, D-5600 Wuppertal 1, Federal Republic of Germany; Study No. T 9055720; 8/29/94); Fifteen Hsd/Win mice/sex were dosed by intraperitoneal (ip) injection with 350 mg/kg of KBR Technical 3023 (batch no. 010393; purity: 99.0%).and 5 animals/sex/time point were euthanized at 16, 24 and 48 hours post-dose. Five animals/sex/group were dosed ip with the vehicle control (0.5% aqueous Cremophor) or 20 mg/kg of cyclophosphamide and euthanized at 24 hours post-dose. The femoral bone marrow was harvested and evaluated for the presence of micronuclei in both polychromatic and normochromatic erythrocytes. One thousand polychromatic erythrocytes were evaluated per animal. Three of the treated animals died (additional animals were included as replacements). Treatment-related signs included apathy, roughened fur, lateral recumbency, spasm, extension spasm, leaping spasm, twitching, difficulty breathing, and slitted eyes. There was no treatment-related increase in the number of micronuclei per 1000 polychromatic erythrocytes. The positive control was functional. **No adverse effect indicated. Study acceptable.** (Moore, 11/12/04)

NEUROTOXICITY

Acute Neurotoxicity

52978-0003; 212243; "An Acute Dermal Neurotoxicity Screening Study with Technical Grade KBR 3023 in Fischer 344 Rats"; (L.P. Sheets; Bayer Corporation, Agriculture Division, Toxicology, Stilwell, KS; Report No. 107467; 10/14/96); The skin of 12 Fischer 344 rats/sex/group was exposed to 0, 200, 600 or 2000 mg/kg of KBR 3023 Technical (batch no. 030693; purity: 97.7% (2/95), 97.4% (8/95)) for 24 hours under an occlusive wrap. Functional observational battery and motor activity evaluations were performed prior to treatment, at 4 hours post-dose and on days 7 and 14. No deaths resulted from the treatment. There was no treatment-related effect upon mean body weights or FOB and motor activity determinations. In the histopathology, no treatment-related lesions were evident. **No adverse effect was indicated. Acute Neurotoxic NOEL:** (M/F) 2000 mg/kg (based upon the lack of treatment-related effects in the highest dose group); **Study acceptable.** (Moore, 9/28/04)

Rat Subchronic Dermal Neurotoxicity Study

52978-0009; 212264; "Subchronic Dermal Neurotoxicity Screening Study with Technical Grade KBR 3023 in Fischer 344 Rats"; (L.P. Sheets, B.F. Hamilton; Bayer Corporation, Agriculture Division, Toxicology, Stilwell, KS; Report No. 107466; 10/9/96); The skin of 12 Fischer 344 rats/sex/group was treated with 0, 50, 100 or 200 mg/kg/day of Technical Grade KBR 3023 (batch no. 030693; purity: 98.1% (6/94), 97.7% (2/95), 97.4% (8/95)) 5 days/week for 13 weeks. The animals wore Elizabethan collars for the duration of the study except during the FOB and motor activity evaluations. Two males in the control group died during weeks 2 and 5. One female each in the control and 100 mg/kg groups died during weeks 2 and 12, respectively. These deaths were not considered to be related to the treatment. There was no treatment-related effect upon the mean body weights or food consumption throughout the study. The ophthalmology examination did not reveal any treatment-related effects. No treatment-related effects were noted in the FOB or motor activity evaluations for weeks 4, 8, and 13. No treatment-related effects were evident in the necropsy examination. The micropathological examination did not indicate any treatment-related lesions. **No adverse effect indicated. Subchronic Dermal Neurotoxicity NOEL:** (M/F) 200 mg/kg/day (based upon the lack of treatment-related effects at the highest dose tested). **Study acceptable.** (Moore, 10/6/04)

SUBCHRONIC STUDIES

Rat Subacute Dietary Toxicity Studies

52978-0004; 212249; “Technical Grade KBR 3023: A Subacute Toxicity Testing Study in the Rat”; (B.S. Wahle; Bayer Corporation, Agriculture Division, Toxicology, Stilwell, KS; Report No. 109817; 9/29/00); Five Sprague-Dawley rats/sex received 0, 1000, 1500, 2000, or 20000 ppm of KBR 3023 Technical (batch no. Pt 030693; purity: 97.1% (7/14/00)) in the diet for 16 (males) or 18 days (females) ((M) 0, 89.8, 140.5, 182.8, 1731.3 mg/kg/day; (F) 0, 108.5, 162.6, 202.2, 1826.0 mg/kg/day). No deaths resulted from the treatment. There were no treatment-related clinical signs or effects upon mean body weights. Mean food consumption was less for both sexes in the 20000 ppm group than for the control group during the first week of the study ($p<0.05$). In the clinical chemistry evaluation, the serum cholesterol levels were elevated for both sexes in the 20000 ppm group over those of the controls ($p<0.05$). In the necropsy examination, the mean absolute and relative liver weights for both sexes in the 20000 ppm group were greater than those of the controls ($p<0.05$). This increase in liver weight was confirmed in the histopathological examination by the incidence of hepatocellular hypertrophy in all of the animals in the 20000 ppm group. Target organ: liver; **No adverse effect indicated. Subacute NOEL:** (M/F) 2000 ppm ((M) 182.8 mg/kg/day, (F) 202.2 mg/kg/day) (based upon the liver hypertrophy noted for the animals in the 20000 ppm group); **Supplemental Study** (study did not adhere to any specified guideline). (Moore, 9/30/04)

52978-0005; 212252; “Technical Grade KBR 3023: A SubchronicToxicity Testing Study in the Rat (5-Week Interval)”; (B.S. Wahle; Bayer Corporation, Agriculture Division, Toxicology, Stilwell, KS; Report No. 110222; 4/5/01); Ten Sprague-Dawley rats/sex received nominal concentrations of 0, 100, 150, 300, or 1000 mg/kg/day of KBR 3023 Technical (batch no. Pt 030693; purity: 97.1% (7/14/00)) in the diet for between 4 and 5 weeks (consumption based on analytical concentrations: (M) 0, 98.9, 152.4, 307.8, 1034.0 mg/kg/day; (F) 0, 120.6, 188.6, 360.2, 1141.4 mg/kg/day). One female in the 1000 mg/kg group was euthanized *in extremis* on day 31. The mean body weight of the 1000 mg/kg males was less than that of the control ($p<0.05$) during the last two weeks of the study. Mean food consumption was less for both sexes in the 1000 mg/kg group than for the control group during the study (NS). In the clinical chemistry evaluation, the serum cholesterol levels were elevated for both sexes in the 1000 mg/kg group over those of the controls (M, $p<0.05$; F, NS). The mean serum triglyceride level was reduced for the 1000 mg/kg males ($p<0.05$). In the necropsy examination, the mean absolute liver weight for the 1000 mg/kg females was greater than that of the controls ($p<0.05$). The mean relative liver weights for both sexes in the 300 and 1000 mg/kg groups were greater than those of the controls ($p<0.05$). This increase in liver weight was confirmed in the histopathological examination by the incidence of hepatocellular hypertrophy in 10 males and 8 females of the 1000 mg/kg group and 9 females in the 300 mg/kg group. In the kidneys, an increased incidence of hyaline droplet formation was noted for the males in the 300 and 1000 mg/kg groups (0: 2/10 vs. 300: 6/10 and 1000: 10/10). Target organs: liver and kidneys; **Possible adverse effect:** hyaline droplet formation in the kidneys (males only)**. Subacute NOEL:** (M/F) 150 mg/kg/day (analytical concentrations: (M) 152.4 mg/kg/day, (F) 188.6 mg/kg/day) (based upon the liver hypertrophy and renal hyaline droplet formation noted for the animals in the 300 mg/kg group); **Supplemental Study** (study did not adhere to any specified guideline). (Moore, 10/1/04)

Rat Subchronic Dietary Toxicity Study

52978-0006; 212254; “Technical Grade KBR 3023: A SubchronicToxicity Testing Study in the Rat (14-Week Interval)”; (B.S. Wahle; Bayer Corporation, Agriculture Division, Toxicology, Stilwell, KS and Experimental Pathology Laboratories, Inc., Hearndon, VA ; Report No. 110223; 4/5/01); Ten Sprague-Dawley rats/sex received nominal concentrations of 0, 100, 150, 300, or 1000 mg/kg/day of KBR 3023 Technical (batch no. Pt 030693; purity: 97.1% (7/14/00)) in the diet for 14 weeks (consumption based on analytical concentrations: (M) 0, 100, 149, 301, 1033 mg/kg/day; (F) 0, 126, 194, 382, 1192 mg/kg/day). One male each in the control and 300 mg/kg groups were euthanized *in extremis*. The causes of death were not considered to be treatment-related. The mean body weights of both sexes in the 1000 mg/kg group were lower than those of the controls (p<0.05). The mean food consumption of both sexes in the 300 and 1000 mg/kg groups was lower than that of the control during the study. No treatment-related effect was evident in the ophthalmology or urinalysis. In the hematology examination, the 1000 mg/kg females demonstrated a lower hematocrit and the 300 and 1000 mg/kg females had lower MCV and MCH values than those of the controls (p<0.05). In the differential white cell count, for the 1000 mg/kg females, the percentage of segmented neutrophils was increased with a corresponding decrease in the percentage of lymphocytes (p<0.05). In the clinical chemistry evaluations, the mean serum cholesterol was increased for both sexes in the 1000 mg/kg group ((M) p<0.05), (F) NS). The triglyceride concentrations for the 300 and 1000 mg/kg males were reduced over that of the control (p<0.05). The absolute liver weights were increased for both sexes in the 1000 mg/kg group ((M) NS, (F) p<0.05). The relative liver weights were increased for this group as well (p<0.05). The relative kidney weights for the 150 and 300 mg/kg males and for both sexes in the 1000 mg/kg were increased over those of the controls (p<0.05). The histopathological examination revealed the presence of liver hypertrophy for both sexes in the 300 and 1000 mg/kg groups ((M) 0: 0/10 vs. 300: 3/10, 1000: 5/10; (F) 0: 0/10 vs. 300: 5/10, 1000: 10/10). A dose-related increase in the severity of the response was noted as well. An increased incidence and severity of chronic nephropathy was noted for the 1000 mg/kg males. Target organs: liver and kidneys. **Possible adverse effect:** hyaline droplet formation in the kidneys (males only). **Subchronic NOEL:** (M/F) 150 mg/kg/day (analytical concentrations: (M) 149 mg/kg/day, (F) 194 mg/kg/day) (based upon the liver hypertrophy noted for the animals in the 300 mg/kg group). **Study acceptable.** (Moore, 10/4/04)

<u>Rat Subchronic Dermal Toxicity Study</u>

52978-0008; 212263; "A Repeated Dose 90-Day Dermal Toxicity Study with Technical Grade KBR 3023 in Rats"; (L.P. Sheets, S.G. Lake; Bayer Corporation, Agriculture Division, Toxicology, Stilwell, KS; Study No. 90-122-HC; 11/1/95); The skin of ten Sprague-Dawley rats/sex/group was exposed to 0, 80, 200, 500 or 1000 mg/kg/day of Technical Grade KBR 3023 (batch no. 19001/90; purity: 99.3% (6/90), 99.2% (3/91)) 5 days/week for 13 weeks. Additional groups of 10 animals/sex/group in the control and 1000 mg/kg groups were dosed in the same manner and then maintained for another 4 weeks after the cessation of dosing as recovery groups. The animals wore Elizabethan collars continuously throughout the study as the exposure to the test material was maintained for the duration of the study period. No deaths occurred during the study. There were no treatment-related effects on mean body weights or food consumption. The hematology examination did not indicate any treatment-related effects. In the clinical chemistry evaluation, the mean serum cholesterol level for the 1000 mg/kg males was greater than that of the controls (p<0.05). In the urinalysis, the mean pH values were lower for both sexes in the 500 and 1000 mg/kg groups than those of the controls (p<0.05). The mean urobilinogen concentration of the 1000 mg/kg males was less than that of the control (p<0.05). In the necropsy examination, the mean absolute and relative liver weights for the 500 mg/kg females and for both sexes in the 1000 mg/kg group were greater than those of the controls (p<0.05). The mean absolute and relative kidney weights for the 1000 mg/kg males and the relative kidney weight for the 500 mg/kg males were greater than that of the control (p<0.05). In the histopathological examination, liver hypertrophy was noted for the males at 200 mg/kg and above and for the females in the 500 and 1000 mg/kg groups ((M) 0: 0/10 vs. 200: 2/10, 500: 9/10, 1000: 10/10; (F) 0: 0/10 vs. 500: 2/10, 1000: 4/10). Necrosis of individual cells in the liver was evident for the 500 and 1000 mg/kg males ((M) 0: 0/10 vs. 500: 3/10, 1000: 4/10). Hyaline degeneration in the kidneys of the 500 and 1000 mg/kg males was also noted (0: 0/10 vs. 500: 7/10, 1000: 8/10). The treated skin of both sexes for all of the treatment levels exhibited effects of acanthosis and glandular hypertrophy. The treated skin of all of the female treatment groups also suffered from hyperkeratosis. The recovery group animals did not demonstrate any treatment-related effects. Target organs: liver and kidneys. **Possible adverse effects:** liver necrosis and hyaline degeneration in the kidneys. **Subchronic Systemic Toxicity NOEL:** (M/F) 80 mg/kg (based upon the incidence of liver hypertrophy in the 200 mg/kg animals); **Subchronic Dermal Irritation NOEL:** (M/F) <80 mg/kg/day (based upon the presence of dermal irritation for the animals in the

80 mg/kg/day group); **Study acceptable.** (Moore, 10/6/04)

METABOLISM STUDIES

Metabolism, Rat

** 0020; 212285; "[Hydroxyethyl-1-^{14}C] KBR 3023: Rat Metabolism Study after Intravenous Injection and after Dermal Application"; (W. Ecker, H. Weber; Bayer AG, Agrochemicals Division, Development Department, Institute for Metabolism Research and Residue Analysis, D-51368 Leverkusen-Bayerwerk, FRG; Study No. M 182 0460-1; 2/27/97); Sprague-Dawley rats of both sexes were dosed either intravenously or dermally with [2-(2-hydroxyethyl-2-^{14}C)] KBR 3023 (batch no. KML2061, specific radioactivity: 24.32 Ci/mole (3.92 MBq/mg), radiochemical purity: >99% (used for iv tests); batch no. KML2169, specific radioactivity: 22.02 Ci/mole (3.55 MBq/mg), radiochemical purity: >99% (used for dermal tests)). In Test Nos. 1 and 2, a total of 5 rats/sex were dosed iv in the tail vein with a single 20 mg/kg dose of the radiolabeled test material. In Test Nos. 3 and 4, a total of 5 rats/sex were dosed iv in the femoral vein with a single dose of 20 mg/kg of the test material. The test material was prepared in physiological saline. In Test Nos. 5 and 6, the skin of a total of 5 rats/sex was exposed to a single dose of 20 mg/kg of the radiolabeled test material for 7 days. In Test Nos. 7 and 8, the skin of a total of 5 rats/sex was treated daily for 2 weeks with 20 mg/kg of unlabeled KBR 3023 technical (batch no. 890814ELB01, purity: 99.1%), followed by exposure to a single dose of 20 mg/kg of the radiolabeled test material for 7 days. In Test Nos. 9 and 10, the skin of a total of 5 rats/sex was exposed to a single dose of 200 mg/kg of the radiolabeled test material for 7 days. Excretion of the radiolabel was predominantly in the urine for both of the iv treatments (75 to 90% of the administered dose). Elimination of the radiolabel in the expired air was negligible even though the radiolabel was on the hydroxyethyl sidechain. Less than one percent of the administered dose was recovered in the body at 48 hours post-dose. In the low dose dermal application studies, approximately 60% of the radiolabel was absorbed. The primary route of excretion was the urine (73 to 88% of the absorbed dose). Pretreatment did not appear to affect the excretion profile. For the 200 mg/kg dermal treatment, the mean percentages of the administered dose which were recovered in the urine and feces ranged between 33 and 40% for the males and females, respectively. The radioactivity recovered in the urine represented 78 and 91% of the total for the males and females, respectively. In the dermal application studies, the absorption half-lives for the males ranged from 1.5 to 1.9 hours. For the females, values demonstrated a greater disparity with a $T_{1/2}$ of 0.8 hours for the single dose 20 mg/kg treatment and a $T_{1/2}$ of 3.4 hours for the single dose 200 mg/kg treatment. The times to maximal plasma concentration ranged between 6 and 8 hours for all of the studies. The maximal plasma concentrations which were achieved appeared to be sex-dependent as the mean values for the males in the low dose dermal treatments were approximately 0.5 ug/ml in contrast to values of 1.6 and 0.8 ug/ml for the females. In the high dose dermal treatment, the values were 4.48 and 11.7 ug/ml for the males and females, respectively. In the iv study (Test Nos. 3 and 4), the 1st , 2nd and 3rd elimination half-lives were 0.9, 5.2 and 45.5 hours for the males and 0.7, 2.8 and 73.0 hours for the females. In contrast, only 1st elimination half-lives were determined for the low dose dermal studies. These half-lives were 35.7 (Test 5) and 41.8 (Test 7) hours for the males and 23.9 (Test 6) and 28.9 (Test 8) hours for the females. For the high dose dermal treatments, the 1st elimination half-lives were 10.9 and 9.1 hours for the males and females, respectively. The 2nd half-lives were 144 and 105 hours, respectively. Analysis of the metabolites revealed that the predominant modifications of the parent compound were phase 1 reactions in which the piperidine ring or the 2-methylpropyl sidechain was hydroxylated or the hydroxyethyl sidechain was oxidized to the carbonyl moiety. Phase 2 conjugation reactions with gluuronide, linoleic or oleic acid constituted a very minor fraction of the recovered metabolites. **Study acceptable.** (Moore, 11/18/04)

Human Dermal Absorption Study

52978-0021; 212289; "A Single Dose Open Label Study to Investigate the Absorption and Excretion of a ^{14}C-Labelled Insect Repellent (KBR 3023) from Two Different Formulations after Dermal Application to Healthy Volunteers"; (S. Selim; Pharma Bio-Research Laboratories, B.V., 9713 G.P. Zuidlaren, The Netherlands (clinical phase) and Biological Test Center, Irvine, CA; Study No. P1092004; 6/20/94); The skin of 6 male human volunteers/group was exposed to 15.0 or 14.7 mg/person (37 uCi/person) of ^{14}C-KBR 3023 (undiluted) or as a preparation in ethanol

(15% (w/w). The subjects were exposed to the test material for 8 hours under a non-occlusive protective wrap. At the end of the treatment period, the treated area was swabbed with isopropyl alcohol and rinsed with the alcohol. The swabs and alcohol were saved for further analysis. Tape stripping in the proximity of the dosing site was performed at 1, 23 and 45 hours post-exposure. Blood samples were drawn at 0, 2, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72 and 120 hours post-application from both the ipsilateral and contralateral arms. Urine was collected prior to dosing and in the following intervals: 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 36, 36 to 48, 48 to 60, 60 to 72, 72 to 84, 84 to 96, 96 to 108, 108 to 120, and 120 to 128 hours post-application. Feces were collected throughout the 128 hour collection period. Most of the applied dose was recovered in the rinsate and on the swabs, protective covering and duoderm at the end of the exposure period, 94.16% and 95.23% of the test material in ethanol and the undiluted test material, respectively. Radiolabel was recovered in the urine of the test subjects (mean values: 3.76% (range: 2.20 to 7.00%) and 1.66% (range: 0.70 to 2.29%) of the applied dose for the solution and undiluted material, respectively). Ninety three to 94% of the label was recovered in the 1st 24 hours. Recovery of radiolabelled compound from the plasma was negligible Absorption of the radiolabelled compound through the skin was quite limited under the conditions of the study. The use of a vehicle (ethanol) seemed to enhance its absorption. **Study supplemental.** (Moore, 3/21/05)